REMARKS

The following remarks are in response to the Examiner's Office Action mailed on June 15, 2007. Claims 8-23, 25-26, 29-32, 37-38, 41-45, 50, 71-73, 102-103, 109-114, 117-119, 121, 124-126, 131-134, 137-138, 141-145, 159, 164-165, 183-184, and 186-187 are canceled without prejudice. Claims 1, 24 and 149 are amended. Claims 1-7, 24, 27-28, 33-36, 39-40, 46-49, 51-60, 62-65, 67-70, 74-79, 81-101, 104-113, 115-116, 120, 122-123, 127-130, 135-136, 139-140, 146-158, 160-163, 166-182, 185, and 188-200 are pending. Reconsideration is respectfully requested in light of the following remarks.

Examiner Interview

Applicants thank the Examiner for the courtesy of an interview on September 19, 2007, during which Applicants attorneys Albert Halluin (Reg. No. 25,227) and Robert Reamey (Reg. No. 50,371); one of the inventors, Nurith Kurn; and Examiner Christopher Babic discussed the issues raised in the outstanding Office Action. Applicants also thank the Examiner for calling Robert Reamey on September 26, 2007 to provide feedback on a proposed claim amendment. At the interview and subsequent discussion, amendments to the claims was discussed. The Examiner indicated that the claims as written might be inadvertently broad, but that if properly amended the claims might be allowable. We agreed to submit amended claim in this response in order to address the current rejections.

Claims Rejections Under 35 U.S.C. §102

Claim(s) 189 and 190 are rejected under 35 U.S.C. 102(b) as being anticipated by Cleuziat et al. (U.S. 5,824,517). The Examiner stated that Cleuziat et al. teaches a kit capable of binding to multiple sites because any primer could bind to a possible template that had multiple binding sites to that same primer sequence. The Examiner stated that under *In re Ngai*, 70 USPQ2d 1862 (Fed. Cir. 2004), where the court found that for the patent at issue in that case, instructions alone did not distinguish the invention from the prior art.

Applicants have amended Claim 189 to indicate that the composite RNA/DNA primers are "designed to randomly bind~~ing~~ to multiple sites within a template DNA." This amendment is

supported in the specification at least in paragraph [0134], so no new matter has been added. Applicants assert that the primers in Cleuziat et al. are not designed to randomly bind to multiple sites within a template DNA. In Cleuziat et al. the primers described are only primers with specific sequences. Cleuziat et al. teaches the use of multiple composite primers, specifically describing some as being located upstream of a sequence of interest, and some being located downstream of a sequence of interest. For the method of Cleuziat, specific primers are used for binding in these locations. Thus Cleuziat et al. does not teach the use of primers that **randomly** bind to multiple sites within a template RNA.

While Cleuziat et al. do not teach composite primers that randomly bind to a target, the Examiner indicates that that there could possibly be a synthetic template made that would intentionally have multiple binding sites to which the composite primers of Cleuziat et al. might bind. Claim 189 has been amended such that the template DNA comprises mitochondrial DNA, chloroplast DNA, DNA-RNA hybrids, genes, chromosomes, plasmids, the genomes of bacteria, yeasts, viruses, viroids, molds, fungi, plants, animals, humans, fragments thereof or cDNA derived therefrom. This amendment is supported in the specification at least in paragraph [0129], so the amendment adds no new matter. Applicants respectfully submit that the Cleuziat does not teach composite primers that are designed to randomly bind to the template DNA defined as above that have not been designed specifically for random binding of targets.

The claims have also been amended such that the term "capable of binding" is replaced with the term "designed to bind".

Applicants believe that for the reasons described above claim 189 is not anticipated by Cleuziat et al., and further that claim 190 is not anticipated as it is dependent on claim 189 and thus contains all of the limitations of claim 189. Thus, Applicants respectfully request that the rejection of claims 189 and 190 be withdrawn.

Claims Rejections Under 35 U.S.C. §103

Claim(s) 84-101, 105-107, 149-158, 160-163, 167-182, 185, 188, 199, and 200 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleuziat (U.S. U.S. 5,824,517) in view of Kass et al. ("Inter-Alu polymerase chain reaction: advancements and applications" Anal Biochem. 1995 Jul

1;228(2):185-93). The Examiner States that Cleuziat et al. teach a method of DNA amplification using a composite primer, and that that Kass et al. teaches the multiplex amplification of multiple loci of a template nucleic acid.

Applicants have amended independent claims 84 and 149 to recite that the composite primer is "designed to randomly bind to to a multiplicity of sites on a DNA template, wherein the sites comprise different nucleic acid sequences." The amendments are provided to clarify the invention. The amendments are supported throughout the specification, at least in paragraph [134] and no new matter has been added.

Applicants submit that the neither Cleuziat et al. nor Kass et al. teach or suggest all of the limitations of the claims. To establish a prima facie case of obviousness, the Examiner must establish that the prior art teaches all of the claim limitations. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Cleuziat et al. does not teach a composite primer that is designed to **randomly bind to a multiplicity of sites**. Cleuziat et al., as described above, teaches primers that bind to upstream and downstream regions of specific sequences. If the method of Cleuziat et al. were to incorporate primers that bind randomly to multiple sites **wherein the sites comprise different nucleic acid sequences,** Applicants submit that Cleuziat's method would not work. In the Cleuziat method the different primers must sit down in specific registration with one another and the use of primers that randomly bind would disrupt the disclosed amplification scheme. Thus, Cleuziat does not teach or suggest primers that randomly bind to a multiplicity of sites on a DNA template wherein the sites comprise different nucleic acid sequences.

Kass also does not teach or suggest a primer that randomly bind to a multiplicity of sites. Kass does not use a composite RNA/DNA primer. The method of Kass for amplifying multiple sites within genomic DNA is directed to **primers containing specific sequences**. For example, Kass says "primers were **designed on the basis of a consensus sequence** that would amplify unique human DNA sequences between *Alu* repeats." Thus Kass does not teach a primer that randomly binds to to a multiplicity of sites on a DNA template, wherein the sites comprise different nucleic acid sequences. Applicants submit that if Kass were to use primers that randomly bind to a multiplicity of sites comprising different nucleic acid sequences it would defeat the purpose of his method which is to selectively amplify only specific portions of the DNA, those which contain, for

example an sites with *Alu* repeats. In addition, even if Cleuziat and Kass had all of the elements, there is no indication of a motivation or suggestion of combining the teachings of Cleuziat et al. and Kass et al. to come up with the present invention.

Thus, for the reasons described above, neither Kass nor Cleuziat teach or suggest all of the limitations. Claims 85-101, 105-107, 150-158, 160-163, 167-182, 185, 188, 199, and 200 are dependent on claims 84 and 149 and are therefore non-obvious as the claims contain the elements of the claims on which they depend. Applicants respectfully request that the rejection of claims 84-101, 105-107, 149-158, 160-163, 167-182, 185, 188, 199, and 200 under 35 U.S.C. §103(a) be withdrawn.

Double Patenting

Claims 1-7, 24, 27-28, 33-36, 39-40, 46-49, 51-60, 62-65, 67-70, 74-79, 81-101, 104-108, 115-116, 120, 122-123, 127-130, 135-136, 139-140, 146-158, 160-163, 166-182,185, and 191-200 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of Kurn et al. (U.S. 6,946,251).

The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to the same general inventive method that employs a first primer comprising a random sequence and a composite amplification primer comprising a RNA and 3' DNA portion that hybridizes to the second primer extension product. The only significant differences between the two claimed method are that claim 9 of '251 is directed to amplification of RNA and claim(s) 1 of the instant method recites a first primer that is hybridizable to a multiplicity of sites within the template sites.

Applicant's respectfully submit that the method disclosed in '251 is significantly different from the method described in the present application, and that the present method is patentably distinct from the method of '251. The Examiner points out that the DNA is an obvious variant of RNA. Applicants respectfully submit that in the context of these amplification methods, RNA and DNA are quite different, and in fact, the method claimed in '251 is directed to amplifying only target RNA, and would not work for a target DNA. The present method is directed to the amplification of DNA.

For example, in '251, claim 9, in step (a), a first primer extension product is made with DNA to create an RNA/DNA hybrid. In step (b), the RNA is cleaved from the hybrid. Step (b) is a critical step in the '251 method, because the cleaving of the RNA makes room on the first primer extension product DNA for the second primer of step (c) which creates the second primer extension product. If instead target RNA, target DNA was used in the method of '251, then step (a) would create a DNA/DNA hybrid (double-stranded DNA). This would create a dead end for the method of '251, because **step (b), the cleaving of the RNA target from the DNA first primer extension product could not be carried out.** If one tried to use an enzyme in step (b) that was analogous to the enzyme recited that cleaves RNA from an RNA/DNA hybrid which would instead cleave DNA, this also would not work because both the target strand and the first primer extension strand would be cleaved. . This discussion illustrates the difference of RNA and DNA in the context of these methods. The '251 method relies on the fact that RNA is different than DNA in order to selectively cleave the template from the first primer extension product in order for the amplification method to proceed. The claims of the present invention only recite the amplification of a **template DNA**, and do not rely on the cleavage of an RNA/DNA hybrid. Thus, since the method claimed in '251 could not be used to amplify the DNA template as in the present invention, DNA is not an obvious variant of RNA in the context of these methods, and the methods of the present invention are patentably distinct from those of '251. Applicants respectfully request that the double patenting rejection to claims 1-7, 24, 27-28, 33-36, 39-40, 46-49, 51-60, 62-65, 67-70, 74-79, 81-101, 104-108, 115-116, 120, 122-123, 127-130, 135-136, 139-140, 146-158, 160-163, 166-182,185, and 191-200 be withdrawn.

CONCLUSION

In light of the remarks set forth above, Applicants believe that the pending claims are under condition for allowance. Applicants respectfully solicit the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 25115-711.201).

Respectfully submitted,

Date 9/28/07 By: 

Albert Halluin
Registration No. 25,227
Robert H. Reamey, Ph.D.
Registration No. 50,371

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Direct Line: (650) 565-3585
Client No. 021971